

Modeling basal ganglia contributions in reward prediction, action selection, and performance

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The basal ganglia (BG) of the forebrain are crucial for voluntary action and cognitive control. The integration of cortical with other inputs within the striatum (the major input structure for the BG) is key for BG function. Medium spiny projection neurons (MSPNs) integrate converging information carried by glutamatergic, GABAergic, dopaminergic and cholinergic afferents. MSPNs are the only striatal neuron types that report decisions to downstream targets. How complex afferent signals interact with intrinsic mechanisms to shape MSPN decisions is unclear. A prominent view is that glutamatergic corticostriatal inputs excite both main classes of striatal MSPNs (D1-SP- and D2-ENK-MSPNs) and that nigrostriatal dopamine (DA) excites "direct-pathway" D1-SP-MSPNs via D1-type DA receptors but inhibits "indirect pathway" D2-ENK-MSPNs via D2-type receptors. This view overlooks many key factors. MSPN membrane voltage fluctuates between a depolarized up-state and a hyperpolarized down-state. Excitatory currents induced by glutamatergic inputs can shift the MSPN membrane from down- to the up-state without eliciting firing, whereas GABAergic inputs from striatal fast-spiking interneurons (FS-INs), and in some cases from neighboring MSPNs, may prevent transition to the up-state. Recent data and simulations show that DA has a state-dependent effect on MSPNs' responses, whereas acetylcholine (ACh) stabilizes the prevailing MSPN state. The complexity of such interactions suggests that only a computational analysis will yield a qualitatively correct understanding. Can Tan and I have developed a biophysics-based computational model to explicate how four major types of synaptic inputs to MSPNs shape striatal information processing. The new model builds upon several of our prior models and the model of Gruber et al. (2003). Gruber et al. (2003) treated DAergic modulation of a few intrinsic currents in D1-SP-MSPNs, but not afferents, and did not treat D2-ENK-MSPNs. Our extended striatal

model can simulate both types of MSPNs, and includes effects not only of DA, but also of ACh and GABA, on intrinsic and afferent-induced currents. Simulations predict that (1) there are large differences in responses of these two classes of MSPNs to GABA and ACh; (2) overall, pausing ACh input by itself is more facilitative than a DA burst by itself; (3) only the combination (probably normative *in vivo*) of a DA burst with an ACh pause can robustly enhance the contrast between the MSPN activation levels elicited by weak and strong cortical inputs; and (4) given two glutamatergic inputs of different magnitudes, regional variations in striatal ACh transmission can bias the D1-SP-MSPNs' responses in favor of one or the other input. Our model predicts an asymmetrical interaction in striatum between attentional salience and the learned motivational value(s) of stimuli. Interesting tradeoffs occur when two stimuli have opposite rank orderings on the two dimensions. Overall, the picture emerging from recent data and modeling shows that the tight temporal coupling of striatal ACh release to DA bursts creates a signal cascade as important for optimizing performance as for optimizing learning. This reveals how the striatum benefits from its own, intrinsic, cholinergic source.